Bandolier 158

Independent evidence-based thinking about health care

On meaning well

A dictionary definition of meaning well would go something like "*marked by good intentions though often producing unfortunate results*". That's one of our problems when folk try to extrapolate from data lacking in quality, or size, or validity. Often, even usually, they mean well. They will tell us that, at that instant, this was the ***best*** information available to guide us.

One trouble is that what was ***best*** was not good enough in the first place, and rapidly became superseded by other, newer, ***better***, data. Another trouble is that the original ***best*** advice becomes set in stone, even when it is plainly wrong. This, it seems to Bandolier, was the case of advice about NSAIDs, coxibs, and the use of low dose aspirin. The original advice was well meaning, but wrong. Considerable subsequent evidence shows that coxib plus aspirin is better than NSAID plus aspirin.

It is the same with ideas and insights. These days we have to be inclusive, and consider all avenues. Carl Sagan pointed out a problem, that *"the well-meaning contention that all ideas have equal merit seems to me little different from the disastrous contention that no ideas have any merit*".

Older old

Bandolier has for some time been intrigued by our aging society, and the impacts it will have on us all. Spurred on by some seemingly hyperbolic claims, we went in search of projections (as we don't have the luxury of waiting around for a century to look at the evidence).

The projected march of the older old shows that there will be many, many, older people in the not too distant future. Some of Bandolier's readers will still be around to deal with this. With luck and fewer chips, Bandolier may be around to complicate matters.

In this issue

NSAIDs, coxibs, aspirin, and GI bleeds

Guidance from various sources has suggested that any protective effect that coxibs have over non-selective NSAIDs is lost in the presence of low dose aspirin. This was based mainly on a meta-analysis of endoscopy studies with few events. A later meta-analysis showed that coxibs plus low dose aspirin produced fewer ulcers than NSAIDs plus low dose aspirin (Figure 1) [1]. What we have lacked is any evidence with real clinical outcomes. A new and very large observational study [2] fills the gap.

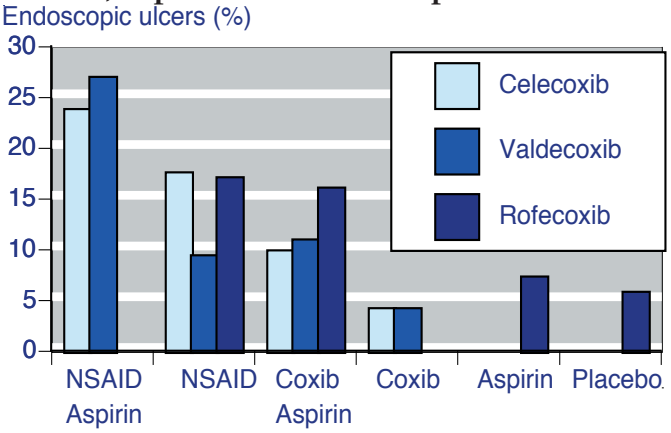
Study

This was a retrospective cohort study based on prescriptions and hospital admission. It covered all persons aged 65 years or older using outpatient and inpatient services from a database with 91% coverage in Quebec. Those filling a prescription for celecoxib or nonselective (ns)-NSAID over 2.5 years ending in 2002 were included in the cohort if they had one year of prescription data and complete coverage for inpatient services. Exclusions were those with prescriptions for both classes of drugs.

The database had comprehensive details of demographic variables, as well as diagnoses and prescription medicines, so that exposure to the drugs of interest could be evaluated. These included gastroprotective agents.

The main outcome was hospital admission for gastrointestinal perforation or bleeding, obtained from hospital discharge summaries using coded information. Such an admission oc-

Figure 1: Endoscopic ulcers in pooled analyses of studies with celecoxib, valdecoxib, and rofecoxib (NSAID = any NSAID; coxib = as in the box; aspirin = low dose aspirin)



curring during an exposure period was attributed to current drug therapy. Where there was overlapping therapy, it was attributed to the drug prescribed last.

A number of analyses were performed for relationships between drug therapies and hospital admission. The main interest was the rates of hospital admission with celecoxib and ns-NSAID, without and with aspirin. Crude results were adjusted for various confounders in the statistical analysis.

Results

The total population in the cohort was 332,491, of whom 71,790 received low-dose aspirin. There were about 700 admissions in almost 70,000 patient years of observation.

Compared with patients taking ns-NSAIDs, those taking celecoxib were more likely to be women, older, and with osteoarthritis. Those taking aspirin had more cardiovascular disease or hypertension than those who did not.

Despite all patients having at least one gastrointestinal risk factor by virtue of age, only about a quarter were receiving gastroprotective therapy at the time of an event, and fewer than a third had a history of having received any such therapy. Higher rates of hospital admission for gastrointestinal perforation or bleeding were seen with older age, in anaemic patients, in those with a prior admission, and with anticoagulant use.

The use of proton pump inhibitor at baseline was associated with a significantly reduced rate of gastrointestinal bleeding compared with non-use (Figure 2). The use of histamine-2 antagonists or misoprostol was not associated with any protection.

Compared with ns-NSAIDs, celecoxib was associated with a substantial reduction in admission for gastrointestinal bleeding (Figure 3). Use of low dose aspirin with ns-NSAID and celecoxib substantially increased the rate of hospital admission, but low dose aspirin with celecoxib was better than low dose aspirin plus ns-NSAID, and about the same as ns-NSAID in the absence of low dose aspirin.

Comment

It really is nice when things come together, and when evidence from randomised trials produces the same answer as evidence from observational studies, especially when both fulfil criteria of quality, validity, and size. The surrogate endpoint of endoscopic ulcers (Figure 1) said that coxib plus aspirin was better than ns-NSAID plus aspirin and about the same as ns-NSAID alone, exactly the same as the findings on hospital admission for gastrointestinal bleeding.

Figure 2: Gastrointestinal bleeding with protective agents plus ns-NSAID vs nonuse of protective agent

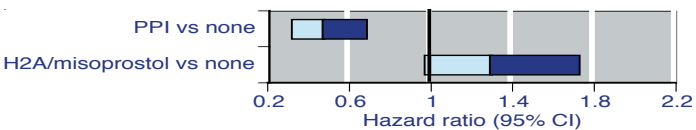
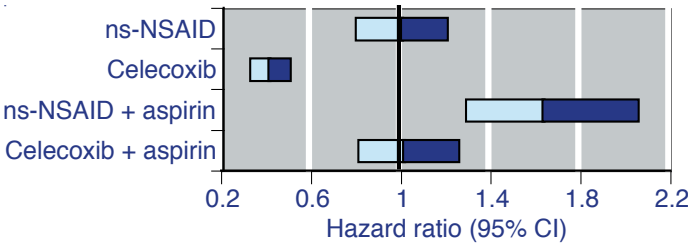


Figure 3: Gastrointestinal bleeding with ns-NSAIDs and celecoxib, without and with low dose aspirin



In addition, we have confirmation that proton pump inhibitors are protective for actual bleeding events, again much as the surrogate endpoint of endoscopic ulcers showed. Additionally, we can dismiss histamine antagonists, confirming what careful reading of the surrogate endpoints used in randomised trials showed.

All in all, it makes for some substantial rethinking of guidance. Celecoxib plus aspirin is better than ns-NSAID plus aspirin. It would be hard to argue to the contrary.

References:

1 RA Moore et al. Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta-analysis of information from clinical trial reports. Arthritis Research & Therapy 2005 7:R644-R665.

2 E Rahme et al. Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study. Rheumatology 2007 46: 265-272.

NSAIDs and coxibs:

OVERALL RISK

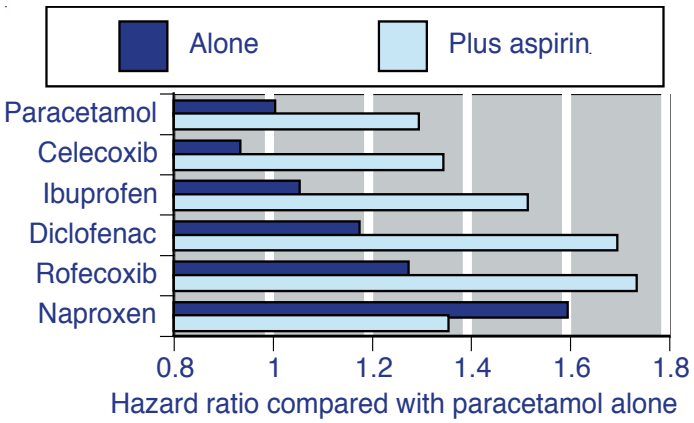
Many folk are spending many hours trying to come up with an equation allowing the overall calculation of gastrointestinal benefit and cardiovascular risk of NSAIDs and coxibs for particular patients. This is something of a forlorn hope given the complexities and arguments over what constitutes the best evidence. A large observational study [1] provides a little more meat.

Study

This retrospective cohort study was based on prescriptions and hospital admission, covering persons aged 65 years or older in Quebec. Those filling a prescription for a coxib or nonselective (ns)-NSAID over 2.5 years ending in 2002 were included in the cohort if they had one year of prescription data and complete coverage for inpatient services. Exclusions were those with prescriptions for both classes of drugs.

The main outcomes were acute myocardial infarction and gastrointestinal bleeding, obtained from hospital discharge summaries using coded information. Calculations were based on the hazard ratio for drugs with or without low

Figure 1: Combined gastrointestinal bleeding and myocardial infarction rates compared with paracetamol without aspirin



dose aspirin compared with paracetamol without aspirin. Crude results were adjusted in the statistical analysis.

Results

The study included 511,000 patients, with 112,000 receiving aspirin. About 22% of patients not receiving aspirin were using gastroprotective agents at some time, with slightly more among aspirin users, but at the time of an event gastroprotective agents were used by about 10% or less.

For both gastrointestinal bleeding and acute myocardial infarction celecoxib was the drug with the lowest hazard ratio. Results for the combined outcome are shown in Figure 1. Without aspirin, naproxen and rofecoxib were associated with significantly greater risk than paracetamol without aspirin. With aspirin, diclofenac and naproxen showed no significantly increased risk.

Comment

What the analyses show is that no drug had significantly increased risk of myocardial infraction compared with paracetamol without aspirin. With aspirin any increased risk had bare statistical significance with low absolute risk increases. Gastrointestinal risk was significantly increased with most drugs except celecoxib, ibuprofen and diclofenac without aspirin. In patients with osteoarthritis, results were generally similar if numerically somewhat higher.

In the overall risk analysis the gastrointestinal risk predominated, in accord with what we know from other observational studies and randomised trials, though, as usual, we have no information about drug doses. The good thing about these observational studies is that they look at patients like ours. The bad thing is that they cannot provide the whole answer because there can be large differences in patients treated with different drugs, and because there can be confounding factors of which we know little.

Reference:
1 E Rahme, H Nedjar. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology 2007 doi:10.1093/rheumatology/kel428

Prostate cancer: timing of therapy

Arguments about cancer treatment are not just about what treatments to use, but when to use the treatments for best effect. There are several points in prostate cancer treatment where this question arises, one of which is in the case of locally advanced prostate cancer. A UK cancer registry showed that around 30% of new presentations of prostate cancer are locally advanced.

Treatment options include watchful waiting, hormone therapy, radical prostatectomy, or radiation with androgen deprivation. A new review [1] examined the evidence for use of hormonal therapy with LHRH agonists or antiandrogens with deferred treatment, when hormonal therapy was used after watchful waiting, radiotherapy, or prostatectomy.

Systematic review

The review used an extensive search strategy in a number of electronic databases to find randomised trials fulfilling the criterion of early versus deferred use of hormone therapy. The primary outcome of interest was overall mortality, with cancer mortality and cancer progression (overall, local and distant) as secondary outcomes.

Results

Eight trials were examined initially, though most results were calculated on seven, with about 6,900 men. All were randomised, and all but one open. Median follow up was typically five to eight years. A number of different hormonal regimens were used, with goserelin with or without flutamide being the most common, and with LHRH agonists featuring in most regimens.

Table 1 shows the results for overall mortality and cancer mortality. There was a significant reduction in mortality associated with early treatment in both cases, and with a similar number needed to treat to prevent one death of about 14. While mortality rates varied between the trials, the reduction in mortality associated with early hormonal therapy was consistent (Figure 1).

In addition to mortality, there were similar reductions of about 30% in rates of overall, local, and distant disease progression.

Table 1: Results for all-cause mortality and cancer mortality

Outcome	Mortality (%) with treatment: Early	Deferred	NNTp (95% CI)
All-cause mortality	37	45	13 (10 to 18)
Cancer mortality	16	23	14 (11 to 19)

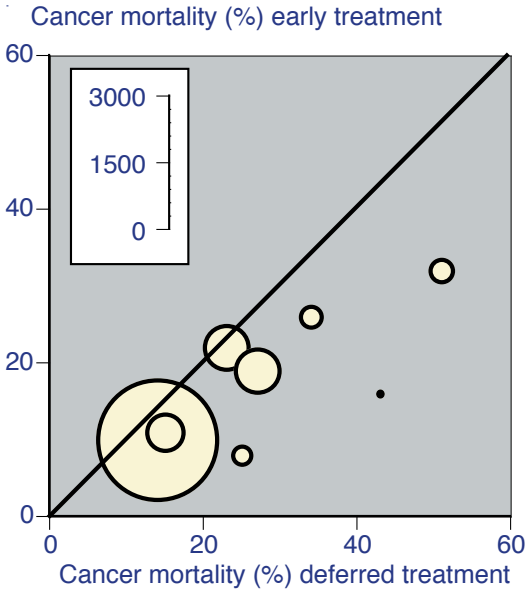
Comment

This appears to be a solid result from a large number of patients studied over many years, and reporting an important, though not the only important, outcome of mortality. The average age of men in these trials was about 70 years at baseline, and relatively high mortality rates are to be expected over five to seven years. Early hormone versus deferred hormone treatment reduced mortality. It is another brick in the wall, allowing oncologists and urologists better to plan treatment of prostate cancer.

References:

1 G Boustead, SJ Edwards. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: a meta-analysis of randomized controlled trials. BJU International 2007 Epub March 6 (doi:10.1111/j.1464-410X.2007.06802.x)

Figure 1: Cancer mortality with early and deferred hormone treatment



Revascularisation choices

Most of us would agree that cardiac ischaemia is not a good thing, and most of us would want someone to do something about it if it was our heart that was affected. In such circumstances most of us would follow the advice of our physician or surgeon about what was the most appropriate way to proceed for us as individuals. We might, though, want to consider what is best on average, and a meta-analysis comparing two approaches provides some information [1].

Systematic review

The review sought studies reporting on minimally invasive direct coronary bypass with left internal thoracic artery anastomosis compared with percutaneous transluminal coronary artery stenting. They had to compare the two interventions for isolated lesions of the left anterior descending artery as a primary intervention. A number of different outcomes were sought, either within 30 days of the procedure, or at maximum follow up.

Results

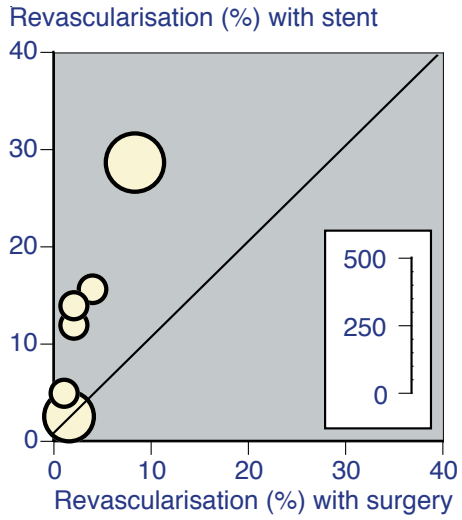
Information was available on eight patient groups in 12 studies, including six prospective randomised studies with 802 patients.

Results for the main outcomes in these six randomised trials are in Table 1. For repeat revascularisation and recurrence of angina there was a greater rate of events with stenting than with surgery, with numbers needed to harm (NNH) of 10 and 6 respectively. Major adverse coronary or cardiovascular

Table 1: Main outcomes of trials comparing coronary artery stents with minimally invasive thoracic artery bypass surgery

Event	Number of trials	Number events/total (%)		Relative risk (95% CI)	NNH (95% CI)
		Coronary artery stent	Minimally invasive thoracic artery bypass		
Repeat vascularisation at maximum follow up	6	57/425 (13)	14/377 (3.7)	3.8 (2.2 to 6.6)	10 (7.4 to 17)
Recurrence of angina	4	77/259 (30)	36/259 (14)	2.1 (1.5 to 3.0)	6.3 (2.4 to 11)
Major adverse coronary or cerebrovascular event	2	48/159 (30)	21/159 (13)	2.3 (1.4 to 3.6)	5.9 (3.9 to 12)
MI within 30 days postoperatively	5	14/378 (3.7)	9/329 (2.7)	1.3 (0.6 to 3.0)	Not calculated
MI at maximum follow up	5	8/327 (2.4)	13/375 (3.5)	0.7 (0.3 to 1.6)	Not calculated
Post procedure stroke of TIA	3	4/209 (1.9)	1/209 (0.5)	2.5 (0.5 to 13)	Not calculated
Mortality at maximum follow up	4	3/179 (1.7)	6/175 (3.4)	0.6 (0.2 to 1.9)	Not calculated

Figure 1: Revascularisation procedures with stents and surgery



events also appeared to be increased with stenting, though this outcome was reported in only two of the trials. There were no differences for myocardial infarction either early or late, or stroke or TIA, or mortality (Table 1).

Figure 1 shows that trials were consistent in having low revascularisation rates with surgery, but had very different revascularisation rates with stents. The two largest trials, in particular, were very different in their outcomes, one showing a large difference, the other none. Repeating the analyses omitting the trial with the largest difference resulted in a higher NNH of 16 that was still statistically significant, while omitting the trial with no difference resulted in a more important NNH of 7.5.

Comment

Given the choice between a relatively simple procedure that would probably allow one to go home and watch the football that afternoon or someone fiddling around inside one's chest, Bandolier would tend to vote for the football. But is that the right choice? This meta-analysis would suggest that it was not.

An accompanying editorial [2] argues that it may well not be the right choice for many, especially those with more severe disease, or more risk factors, like diabetics. It points out that the trials were limited in follow up, so limiting any observation of mortality benefit (and there were only nine deaths observed in 350 or so patients), and that trials usually recruited patients with less severe conditions.

When stents come with a 1 in 10 chance of having a second procedure, and a 1 in 3 chance of recurrence of angina, the football choice does seem less attractive.

References:

1 O Aziz et al. Meta-analysis of minimally invasive internal thoracic artery bypass versus percutaneous revascularisation for isolated lesions of the left anterior descending artery. BMJ 2007 334: 617-621.

2 DP Taggart. Coronary revascularisation. BMJ 2007 334: 593-594.

Lignocaine, spinal anaesthesia, and neurological complications

Spinal anaesthesia has been used now for over a century, and a number of local anaesthetics is available. Increased employment of day case surgery has led to increased use of spinal anaesthesia, especially with rapid onset and short duration of action, allowing patients to go home sooner.

Spinal anaesthesia is associated with relatively low rates of neurological complications, some of which may be severe and permanent. These may be a result of a combination of needle injury, unusual anatomy, and effects of anaesthetic drugs.

Transient neurological symptoms refer to those appearing from a few hours to 24 hours after full recovery from uneventful spinal anaesthesia. They include pain, which can be severe, originating from the gluteal region and radiating to the lower extremities. A systematic review [1] questions whether these symptoms are associated with a particular local anaesthetic, and especially lignocaine (or lidocaine, depending where in the world you are).

Systematic review

This review sought randomised and pseudo-randomised trials appearing as full publications in adults receiving spinal anaesthesia, including pregnant women. The follow up period for transient neurological symptoms had to be at least 24 hours. At least one study arm had to have used lignocaine.

Results

Fifteen studies were included, with 1,439 patients in 18 comparisons, and with information on 1,437 patients. Rates of transient neurological symptoms were consistently higher with lignocaine than with other local anaesthetics, with the possible exception of mepivacaine (Figure 1; Table 1).

Figure 1: Neurological symptoms with lignocaine and other local anaesthetics

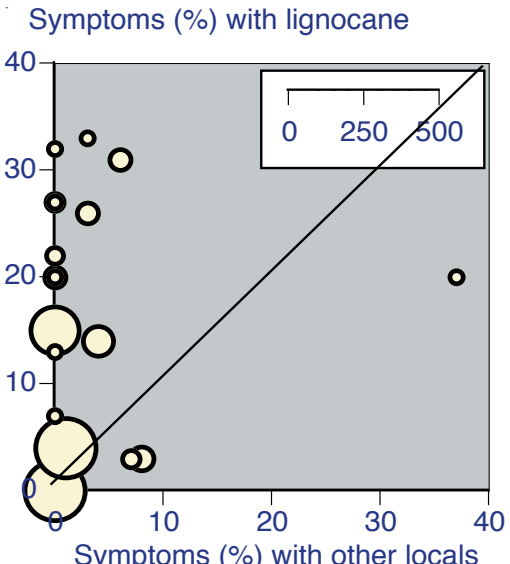


Table 1: Results for transient neurological symptoms with individual local anaesthetics

Drug	Trials	Patients		
		N	With symptoms	Percent with symptoms
Lignocaine	18	704	97	14.0
Bupivacaine	7	291	3	1.0
Prilocaine	4	217	4	1.8
Mepivacaine	3	100	14	14.0
Procaine	2	65	2	3.1
Ropivacaine	1	30	0	0.0
Levobupivacaine	1	30	0	0.0

The typical description was of bilateral pain in buttocks, thighs, and legs, with visual analogue scores varying from 2 to 9 on a 10 point score. Pan usually disappeared by the second day, and the maximum duration was five days. No patient with transient neurological symptoms was reported to have any permanent neurological sensory or motor deficits.

Overall, 14% of patients given lignocaine had transient neurological symptoms compared with 3.1% with any other local anaesthetic, giving a number needed to harm of 9 (95% CI 7 to 13).

Comment

Anaesthetists may want to look at these data much more closely. There is considerable clinical heterogeneity between the trials, in terms of patients, their position during operation, the size and cut of the needles used, the placing of the anaesthetic, whether it was hyperbaric, the strength of the local anaesthetic, to name just some of the issues they will have. Definition of symptoms may be another. Whether any of these points turns out to be crucial is another matter, but people have looked at some of them, and found, for instance, that the incidence of neurological symptoms did not vary with lignocaine concentration.

Moreover, however you look at these data, there are issues of trial quality (most were open) and the lack of numbers, and the reasons for the large spread of results with lignocaine, from 0 to over 30%. This suggests either some technical issue, or some quality issue of trial reporting that this review did not explain.

We must also remember that significant and long lasting neurological damage after spinal anaesthesia is a very rare event, with lignocaine or any other local anaesthetic. So these adverse events are transient, an important fact. All of which, of course, makes this an interesting learning example, and one that should have legs.

Reference:

1 D Zaric et al. Transient neurological symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. Cochrane Database of Systematic Reviews 2005 issue 4.

Morning or evening statins

As long ago as Bandolier 88 the question was asked whether taking a statin in the evening really was better than taking a statin in the morning to produce more cholesterol lowering at the same dose. A new review [1] allows a better answer.

Review

Although not described as a systematic review [1], it tells us that a number of electronic databases were searched for clinical trials that examined morning and evening dosing of statins. Studies were not restricted by the type of subjects included, so patients with hypercholesterolaemia and healthy adults were allowed for inclusion.

Results

The review found seven trials, and reports the percentage reduction in low density lipoprotein cholesterol found with each. All but two of the studies enrolled patients with hypercholesterolaemia. One trial did not have information and another trial was missed in the search.

Table 1 shows the summary data for the percentage difference in evening minus morning statins, and includes two simvastatin trials at doses of 10-20 mg and 10-40 mg that did not have data in a form to be included in Figure 1. The largest average difference (weighted by size) was for simvastatin at 8.7%. Lovastatin had only been studied in 10 patients. For the other three statins there was no large difference in low density lipoprotein cholesterol between evening and morning dosing.

Figure 1 shows the percentage reductions for each comparison, with the two simvastatin comparisons, where there was the largest difference as dark symbols. In both of these comparisons the dose of simvastatin was low, 2.5 mg and 5 mg respectively. Other studies used clinically more relevant doses of atorvastatin, lovastatin, pravastatin, and rosuvastatin.

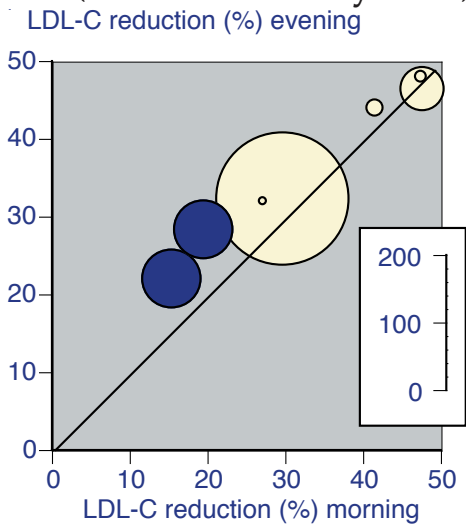
Comment

Both simvastatin and lovastatin have relatively short half lives, while the other three statins have much longer half lives. It seems that the theory of a greater bang per dose with evening dosing for short half life statins holds up.

Table 1: Pooled results for individual statins

Statin	Dose (mg)	Number of patients	Evening - morning LDL-C (%)
Simvastatin	2.5-40	254	8.7
Lovastatin	40	10	5.3
Pravastatin	40	196	3.0
Rosuvastatin	10	24	2.9
Atorvastatin	40	80	-0.4

Figure 1: Percentage reduction in LDL-cholesterol from baseline with evening and morning statin doses (simvastatin dark symbols)



Is knowing that some statins are better taken at night important? The answer is probably that it is. If there is to be considerable statin switching (mainly to simvastatin) to save money (Bandolier 157), then it makes sense to emphasise to patients that evening use is better. The last thing we want is to have people switching back again, which is the way to lower adherence.

If adherence is thought to be a problem, and where most tablets are taken in the morning, one of the longer half-life statins taken in the morning may be a better option for optimum cholesterol lowering.

References:

1 R Plakogiannis, H Cohen. Optimal low-density lipoprotein cholesterol lowering – morning versus evening statin administration. Annals of Pharmacotherapy 2007 41: DOI 10.1345/aph.1G659

March of the older old

Bandolier has for some time been intrigued by sweeping predictions of increases in the number of older people in the population. While this is likely to be true, it is always worth looking at the numbers behind the headlines.

UK projections

Figures for the UK as a whole, or its constituent nations, can be found at the website of the Government Actuaries Department (GAD; [1]). The site has some addition useful background information to help us make sense of the numbers. Downloadable tables show the predicted number of people of various ages in the population between about 2005 and 2074.

For the ages of 0-60 years, the total number of people in the UK populations remains remarkably stable over those 70 years or so, according to the projections and without taking much account of immigration. Over the period the total population growth of about 10 million, from 60 to 70 million, comes from increasing numbers of over-65s, whose numbers double over the period, and increase from 16% to 28% of the population (Table 1; Figure 1).

Almost 40% of the increase comes from an increase in the numbers of the oldest old, here defined crudely as 85 years or older. This group quadruples in number over the period, and increases from 2% to 5% of the population (Table 1; Figure 1).

The most spectacular growth is in the number of centenarians. Over the 70 years of the projections, their number increases from 11,000 in 2007 to over a third of a million by 2070, and increase of almost 32 times (Table 1; Figure 2). Most of this increase comes in the later part of the period.

Of course, with this comes an increase in average life expectancy, by a few years more than present.

US projections

Figures for the USA can be found in their Census Bureau [2] in a variety of forms and in great detail. The number aged 65 years and older in the USA will almost double from 37 million in 2006 to 63 million by 2025, and there will be a third of a million over the age of 100 years by 2020.

Other places

The way in which population demographics will change in different parts of the world will not all be the same as in

Figure 1: Total number of people aged 65 years and older and 85 years and older in the UK population between 2007 and 2074

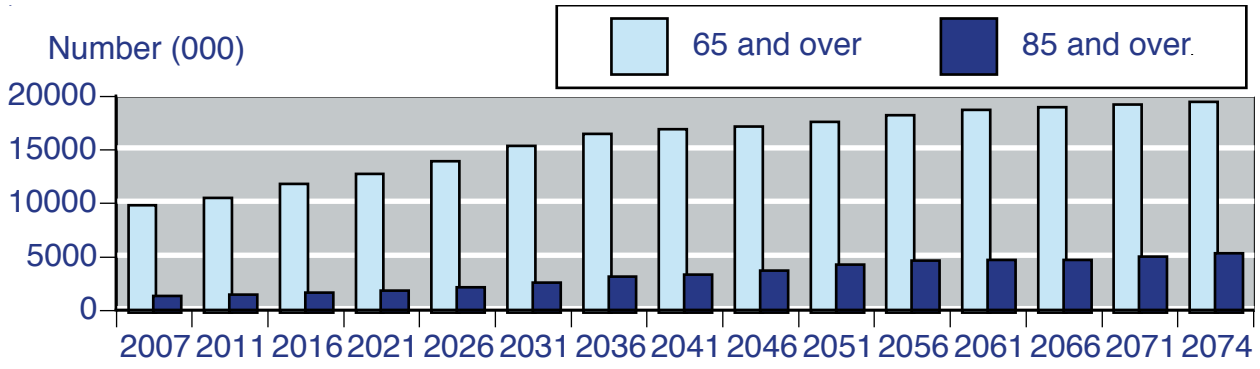
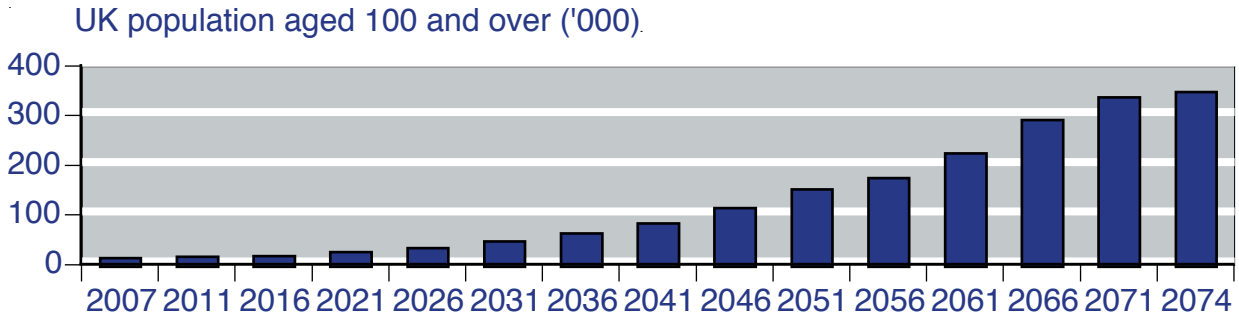


Figure 2: Total number of people aged 100 years and older in the UK population between 2007 and 2074



the UK and USA. A one-stop shop to examine population projections is at a United Nations site [3], with more details on population aging at another [4].

Comment

Some of the impact of these major changes will fall on people alive and in practice today. A child born in 2007 will see a very different world when entering his or her eighth decade in 70 years time. It is too easy to try and list the potential burdens that such changes will place on society, because the list becomes too long too quickly.

Perhaps two things are obvious. Although total life expectancy is increasing, the number of expected years in good health is not increasing so rapidly and there is a significant proportion of later years of life that may well not be spent in good health. A consequence will be a large increase in demands for healthcare, and there is at least the potential for a substantial shortfall between demand and supply, which will make any such problems we have now trivial by comparison.

The second obvious point is that there is much to be gained by vigorous promotion of healthy lifestyle, and a punitive attitude to an unhealthy lifestyle. The supply gap can be reduced by having more fit elderly people, and especially fit older old.

References:

1 http://www.gad.gov.uk/
2 http://www.census.gov/
3 http://esa.un.org/unpp/
4 http://www.un.org/esa/population/publications/aging99/aging99.htm

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Table 1: Total number of older people in the UK population between 2007 and 2074

Year	Total population (000)	Aged 65 and over			Over 85			100 and over		
		Population (000)	Percent of total	Growth (2007=1.0)	Population (000)	Percent of total	Growth (2007=1.0)	Population (000)	Percent of total	Growth (2007=1.0)
2007	60,821	9,794	16.1	1.00	1,280	2.10	1.00	11	0.02	1.0
2011	61,892	10,489	16.9	1.07	1,407	2.27	1.01	14	0.02	1.3
2016	63,304	11,789	18.6	1.20	1,584	2.50	1.24	16	0.03	1.5
2021	64,727	12,740	19.7	1.30	1,813	2.80	1.42	23	0.04	2.1
2026	66,002	13,922	21.1	1.42	2,117	3.21	1.65	32	0.05	2.9
2031	67,013	15,340	22.9	1.57	2,544	3.80	1.99	45	0.07	4.1
2036	67,766	16,457	24.3	1.68	3,079	4.54	2.41	61	0.09	5.5
2041	68,353	16,894	24.7	1.73	3,305	4.84	2.58	81	0.12	7.4
2046	68,842	17,138	24.9	1.75	3,683	5.35	2.88	113	0.16	10.3
2051	69,252	17,605	25.4	1.80	4,241	6.12	3.31	150	0.22	13.6
2056	69,580	18,236	26.2	1.86	4,626	6.65	3.61	173	0.25	15.7
2061	69,858	18,682	26.7	1.91	4,632	6.63	3.62	223	0.32	20.3
2066	70,148	18,940	27.0	1.93	4,666	6.65	3.65	290	0.41	26.4
2071	70,481	19,235	27.3	1.96	4,989	7.08	3.90	336	0.48	30.5
2074	70,691	19,432	27.5	1.98	5,283	7.47	4.13	346	0.49	31.5